REMARKS

The following remarks and accompanying information disclosure statement and references are submitted in response to the Office Action of July 1, 2005. Currently Claims 38-60 and 73-81 are pending, with Claims 40-43, 55-59, 61-72 and 77-80 withdrawn and Claims 38, 39, 44-54, 59, 60, 73-76 and 81 standing rejected. Reconsideration is respectfully requested.

I. Interview

Applicants thank Examiners Young and Kishore for their time and consideration during an interview held at the USPTO on November 6, 2004, during which the present invention and search strategies were discussed.

II. Rejection under 35 USC § 103

Claims 38, 39, 44-54, 59, 60, 73-76 and 81 stand rejected under 35 USC § 103 based on the hypothetical combination of US Patent 6,096,728 to Collins et al. and US Patent 5,206,023 to Hunziker. Applicants respectfully traverse this rejection. Before addressing the cited art, the following brief overview of the invention is presented.

A. Overview of the Invention

Articular cartilage is a specialized extracellular matrix that is produced and maintained by metabolically active articular chondrocytes. The maintenance of a normal, healthy extracellular matrix reflects a dynamic balance between the rate of biosynthesis and incorporation of matrix components, and the rate of degradation and subsequent loss of these components from the cartilage into the synovial fluid. While the regulatory mechanisms that underlie the matrix homeostasis are not fully understood, they are clearly altered in inflammatory and non-inflammatory joint diseases and in response to joint trauma, such that the rate of matrix breakdown exceeds the rate of new synthesis of matrix components. Matrix homeostasis is generally regarded to represent a dynamic balance between the effects of catabolic cytokines and

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anabolic cytokines, including growth factors. The present invention recognizes the need to re-establish and preserve this balance for an optimized cartilage protective (chondroprotective) effect.

Independent Claim 38 is directed to a method of inhibiting cartilage degradation in a joint of a patient, by delivering a composition of chondroprotective agents in solution. The composition includes a therapeutically effective amount of a first chondroprotective agent that is an anabolic chondroprotective agent and a therapeutically effective amount of a second chondroprotective agent that is an inhibitor of cartilage catabolism. This composition is delivered locally to the joint. The method of independent Claim 73 is similar to that of independent claim 38, but also calls for the composition to be delivered to the joint within an acute phase following trauma to the joint.

The present invention thus provides a method for inhibiting cartilage degradation that addresses both sides of the cartilage matrix homeostasis equation: an anabolic chondroprotective agent to promote cartilage synthesis together with an inhibitor of cartilage catabolism to inhibit cartilage break down. This approach has not previously been utilized in the treatment of cartilage disorders (e.g., rheumatoid arthritis, osteoarthritis), which instead relies on the administration of inhibitors of cartilage catabolism, such as tumor necrosis factor–α (TNF-α) inhibitors or interleukin–1 (IL-1) inhibitors. Growth factors are also being developed for use as anabolic promoting agents in treating cartilage disorders. However, these two distinct, parallel paths have conventionally been followed *separately* as *alternative* approaches. Applicants are aware of no prior art that discloses the administration of compositions including both a cartilage catabolism inhibitor and a promoter of cartilage anabolism to the joint to inhibit cartilage degradation, as claimed in the present invention, to address both of the noted processes involved in the maintenance of cartilage health.

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B. Cited Art

The Office Action cites Collins '728 for the disclosure of the administration of an IL-1 inhibitor with additional agents such as MAPK inhibitors or anti-inflammatory agents for the treatment of osteoarthritis, psoriatic arthritis and/or rheumatoid arthritis. A review of this reference confirms that the agents disclosed for concurrent administration with the IL-1 inhibitor are anti-inflammatory agents, corticosteroids, slow acting antirheumatic drugs or disease modifying drugs (Column 28, lines 20-37 et seq.). The additional agents disclosed do include catabolic inhibitory agents, such as COX-2 inhibitors (Column 32, lines 21-34) and TNF inhibitors (Column 32, line 51 – Column 34, line 5). However, as acknowledged in the Office Action, Collins '728 does not disclose the inclusion of a growth factor or other anabolic agent with the IL-1 inhibitor. Thus while this reference may be viewed as disclosing multiple catabolic inhibitory agents, it does not disclose or suggest in any way administration of a solution including both a catabolic inhibitor and an anabolic chondroprotective agent.

The Office Action relies on Hunziker '023 for the disclosure of fibroblast growth factors (FGF) to treat defects in cartilage. While Hunziker '023 does disclose the use of anabolic promoting agents, it does not disclose or suggest in any way the administration of catabolic inhibitory agents together with the anabolic promoting agents. Rather, Hunziker '023 is solely directed to inducing repair and regeneration (Column 3, lines 27-31).

C. No *Prima Facie* Case of Obviousness

Applicants respectfully submit that the hypothetical combination of Collins '728 and Hunziker '023 does not result in a *prima facie* case of obviousness. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990); MPEP § 2143.01. In this case, Collins '728 is an example of the inhibition of

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cartilage catabolism. Hunziker '023 is an example of the promotion of cartilage synthesis. The references reflect two *different* approaches to treating cartilage disorders, but neither suggests the novel approach of the present invention, which is to combine both approaches in an effort to achieve cartilage matrix homeostasis. In the absence of such a suggestion in the prior art, Applicants respectfully submit that the rejection must be withdrawn.

D. Unexpected Results

Even if the Examiner should none-the-less combine the cited references (which Applicants submit would be improper in the absence of a suggestion in the cited art), Applicants provide evidence herewith that demonstrates unexpected results obtained from the present invention, which results strongly support the nonobviousness of the present invention. At the time of filing of the complete disclosure in the priority application on which the instant application is based (Serial Number 60/144,904 filed July 21, 1999), it was generally accepted that elevated levels of multiple cytokines such as IL-1 and TNF-α are responsible for the disrupted matrix homeostasis that is the hallmark of osteoarthritis (addressed herein by way of example). The effect of these cytokines is two-fold. First, they induce the catabolic processes that are responsible for the degradation of the cartilage matrix. Various anti-catabolic agents had been identified that reverse or slow this destruction. However, the second effect of these cytokines is that they inhibit both the basal and growth factor induced synthesis of matrix components, thus preventing any repair of the damaged cartilage. Thus, osteoarthritic chondrocytes or IL-1 activated chondrocytes do not respond well to anabolic growth factors such as IGF-1. *See, e.g.*, Loeser et al., *Arthritis & Rheumatism* 43:9 2110-2120, 2000. Hence, it would have been considered unlikely that these growth factors by themselves would have any significant disease modifying effect.

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An unexpected result of the method claimed by Applicants is that catabolic inhibitory agents have the potential to *not only inhibit inflammation and matrix degradation, but to also restore the ability of the diseased chondrocytes to respond to anabolic growth factors*, and thus permit repair of the damaged cartilage. This surprising result has been demonstrated by a series of recent papers published by others well after the filing of the above-noted priority application. Applicants have included this non-prior art on the listing in the citation of information cited concurrently herewith together with copies of these references, and summarize several examples of this supporting work below. Each of these papers provides results from studies of combinations of anabolic promoting factors with catabolic inhibitory factors and strongly supports the invention of Independent Claims 38 and 73, as well as claims dependent therefrom.

Reference O01735 (Studer et al, *J Orthopaedic Research* 21: 914-921, 2003) describes the unexpected observation that blocking the production of nitric oxide partially reverses the IL-1 suppression of IGF-1 stimulated proteoglycan synthesis. The initial studies demonstrated that IL-1 suppressed the IGF-1 stimulation of proteoglycan synthesis in slices of rabbit articular cartilage, and that this suppression could be partially reversed by blocking the inducible form of nitric oxide synthase (iNOS) with L-NMA (Figure 1). Nitric oxide synthase inhibitors such as L-NMA are inhibitors of cartilage catabolism as presently claimed (*see, e.g.*, Claim 54). L-NMA by itself had no effect on the IL-1 suppression of proteoglycan synthesis. The second set of studies demonstrated that IGF-1 (an anabolic chondroprotective agent as presently claimed, *see e.g.*, Claim 53) will not stimulate proteoglycan synthesis in human osteoarthritic chondrocytes (Figure 4). Nor was any stimulation of proteoglycan synthesis in human osteoarthritic chondrocytes obtained with L-NMA (Figure 4). *However, the combination of IGF-1 and L-NMA surprisingly resulted in a significant induction of proteoglycan synthesis* (Figure 4). L-NMA

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could also increase the responsiveness of IL-1 activated chondrocytes to 5% fetal bovine serum (FBS) (but was ineffective in combination with TGF-β under the conditions studied) (Figure 5).

Reference O01733 (Studer et al, *Arthritis Research and Therapy* 6: R56-R64, 2004) describes the effect of three catabolic inhibitory agents on the IL-1 suppression of growth factor induced mitogenesis in primary cultures of rabbit articular chondrocytes. The catabolic inhibitory agents (as claimed, *see, e.g.*, Claim 54) studied included a MAP kinase (MAPK) inhibitor, a nitric oxide synthase inhibitor and a cyclooxygenase-2 (COX-2) inhibitor. IL-1 suppressed the proliferation that is normally induced by IGF-1 (a claimed anabolic agent) or 5% fetal calf serum (FCS) and *this suppression was surprisingly reversed* by the p38 MAPK inhibitor SB 203580 (Figure 4). Inhibition of nitric oxide synthesis with L-NMA *also reversed* the IL-1 suppression of IGF-1 and FCS induced proliferation (but had no effect in combination with TGF-β under the conditions studied) (Figure 7). Inhibition of COX-2 activity with SC-58125 had little effect on the IL-1 suppression of growth factor induced proliferation under the conditions studied (Figure 9).

Reference O01734 (Studer et al, *J Orthopaedic Research* 23: 454-461, 2005) demonstrated that two claimed anti-catabolic agents, a p38 MAPK inhibitor and a COX-2 inhibitor, can restore the ability of IL-1 activated human osteoarthritic chondrocytes to respond to a claimed anabolic agent, TGF-β. The first anabolic parameter to be measured was chondrocyte proliferation. IL-1 activated osteoarthritic chondrocytes did not proliferate in response to TGF-β, IGF-1, or FCS (Figure 3). Although inhibitors of p38 MAPK (SB-203580) and COX-2 (SC-58125) had a slight proliferative effect on their own, *a significantly larger proliferative effect was unexpectedly observed when these inhibitors were combined with TGF-β or FCS* (Figures 1 & 3). The second anabolic parameter to be measured was proteoglycan synthesis. *The combination of the COX-2 inhibitor (SC-58125) and TGF-β stimulated*

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proteoglycan synthesis whereas TGF-β had no effect on its own and SC-58125 by itself led to a slight decrease in proteoglycan synthesis (p. 457). In contrast, the combination of TGF-β and the p38 MAPK inhibitor was not effective at inducing proteoglycan synthesis under the conditions studied (Figure 4). The third marker that was measured was TIMP-1 (tissue inhibitor of metalloproteinases), which is an endogenous inhibitor of the matrix metalloproteinases that mediate degradation of the cartilage matrix. IL-1 suppressed TIMP-1 expression and this suppression was partially reversed by the p38 MAPK inhibitor (SB 203580), the COX-2 inhibitor (SC-58125), and by TGF-β (Figure 5). However, *the effect of the combination of TGF-β and SB-203580 was surprisingly greater than even the additive effects of both agents alone*, and under these conditions the production of TIMP-1 was greater than that observed in control cultures that were not treated with IL-1.

Taken together, the above noted non-prior art references evidence a surprising result of the present claimed invention. When administered together with an anabolic chondroprotective agent, catabolic inhibitory chondroprotective agents not only suppress cartilage catabolic processes, *but may significantly reverse the anti-anabolic effect of catabolic mediators*. This result was neither disclosed nor predicted in the art of record, and strongly supports the patentability of the claimed invention.

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III. Closure

In view of the above remarks, reconsideration and passage of all of claims 38-60 and 73-81 to issue is respectfully requested. Should the Examiner have any remaining questions or concerns, he is invited to telephone the undersigned attorney.

Respectfully Submitted,

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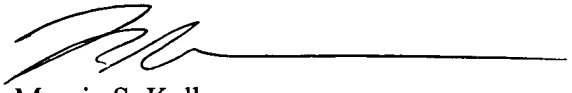

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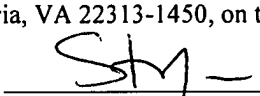

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